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Review

Significance of sphingosine-1-phosphate in cardiovascular physiology and pathology

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ABSTRACT

Sphingosine-1-phosphate (S1P) is a signaling lipid, synthetized by sphingosine kinases (SPHK1 and SPHK2), that affects cardiovascular function in various ways. S1P signaling is complex, particularly since its molecular action is reliant on the differential expression of its receptors (S1PR1, S1PR2, S1PR3, S1PR4, S1PR5) within various tissues. Significance of this sphingolipid is manifested early in vertebrate development as certain defects in S1P signaling result in embryonic lethality due to defective vasculo- or cardiogenesis. Similar in the mature organism, S1P orchestrates both physiological and pathological processes occurring in the heart and vasculature of higher eukaryotes. S1P regulates cell fate, vascular tone, endothelial function and integrity as well as lymphocyte trafficking, thus disbalance in its production and signaling has been linked with development of such pathologies as arterial hypertension, atherosclerosis, endothelial dysfunction and aberrant angiogenesis. Number of signaling mechanisms are critical – from endothelial nitric oxide synthase through STAT3, MAPK and Akt pathways to HDL particles involved in redox and inflammatory balance. Moreover, S1P controls both acute cardiac responses (cardiac inotropy and chronotropy), as well as chronic processes (such as apoptosis and hypertrophy), hence numerous studies demonstrate significance of S1P in the pathogenesis of hypertrophic/fibrotic heart disease, myocardial infarction and heart failure. This review presents current knowledge concerning the role of S1P in the cardiovascular system, as well as potential therapeutic approaches to target S1P signaling in cardiovascular diseases.

1. Introduction

1.1. Sphingosine-1-phosphate- biosynthesis, localization and general function

Although limited biological relevance has been attributed to lysophospholipids for many years, the finding that sphingosine-1-phosphate (S1P) has the ability to act as a ligand for G protein-coupled receptors (GPCRs) has opened up novel research areas in lipid biology [1]. Currently, it is widely acknowledged that S1P possesses pleiotropic functions and orchestrates many cellular processes including cell growth, proliferation, migration and apoptosis [2–5]. S1P derives from phospholipids building up cell membrane bilayer. Sphingomyelin is enzymatically metabolized by sphingomyelinase to produce ceramide which is cleaved by ceramidase to form sphingosine [6]. Sphingosine-1-phosphate is produced by the phosphorylation of sphingosine by sphingosine kinase 1 (SPHK1) or sphingosine kinase 2 (SPHK2). The level of S1P is further controlled through its irreversible degradation to hexadecenal and ethanolamine phosphate by S1P lyase (SPL), as well as through reversible dephosphorylation by sphingosine-1-phosphate phosphatases (SPPs) or broad-specificity lipid phosphate phosphatases (LPPs), and the latter are the only enzymes that are able to degrade extracellular S1P [6,7].

S1P predominantly exists in the blood as it is mainly produced by erythrocytes, endothelial cells (ECs) and, less efficiently, by activated platelets [8,9]. Erythrocyte- and platelet-borne S1P is transported extracellularly *via* the major facilitator superfamily transporter 2b (Mfsd2b), while ECs export S1P *via* the sphingolipid transporter 2 (Spns2) [10,11]. Studies reveal that both SPHKs are responsible for the generation of the plasma S1P fraction. It has been demonstrated that pharmacological and genetic inhibition of Sphk1 reduces plasma S1P level by approximately half [12,13]. Surprisingly, *Sphk2* knockout mice have significantly higher S1P levels in plasma and in blood cells as compared to wild-type animals [14,15]. This might be attributed to the

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fact that murine Sphk2 plays a role in the redistribution of erythrocyte-borne S1P to ECs. More specifically, S1P produced by erythrocytes is dephosphorylated by Lpp1 to produce sphingosine, which is then taken up by ECs and re-phosporylated by Sphk2 to form intracellular S1P. Thus, the lack of Sphk2 in mice results in S1P congestion in the blood [14].

The concentration of S1P in the plasma ranges between 0.1 and 1.2 μM [10] (it is approximately 1/4 lower in the lymph as compared to levels in the plasma) [16], while a smaller concentration of S1P has been observed in tissues (0.5–75 pmol/mg) [17]. In general, there exists a large S1P gradient between the blood/lymphatic circulatory system and interstitial fluids [16]. To enhance the aqueous solubility of the lipid in the blood and lymph, S1P is carried by various chaperone proteins [18]. More than 50% of S1P is transported by high density lipoproteins (HDLs). The remaining amount is bound to albumin (30–40%), and less than 10% is transported by low density lipoproteins (LDLs) and very low density lipoproteins (VLDLs) [7]. Importantly, Murata and colleagues showed that HDL contains a much higher S1P concentration than LDL [19], while Christoffersen et al. found that apolipoprotein M is responsible for the binding of S1P to HDL [20]. Interaction of S1P with plasma proteins seems to lower its bioavailability [21]. The type of S1P carrier affects its activity and metabolism [7]. It has been observed that the half-life of HDL-bound S1P is 4-fold higher than that of albumin-bound and such effect is due to prevention of S1P degradation by ecto-phosphatases [22]. Moreover, the type of carrier also has an impact on S1P receptor (S1PR) signaling [23]. Due to the fact that HDL and S1P share common functional features, S1P is believed to be one of the main determinants of HDL action [24,25].

1.2. Sphingosine kinases- structure, localization and function

Two isoenzymes responsible for S1P biosynthesis, SPHK1 and SPHK2, originate from two separate genes located on chromosomes 17 and 19, respectively [26]. SPHKs consist of a C-terminal region and an N-terminal region containing an ATP-binding site and a sphingosine recognition site. Human SPHKs share 80% similarity with each other and almost the entire SPHK2 polypeptide sequence aligns with the sequence of SPHK1. However, the SPHK2 isoform is considerably larger due to the presence of two additional regions *i.e.* first one at the N-terminal end and the other, proline-rich region, within the central part. Additionally, several splicing variants of SPHK1 and SPHK2 which differ in length and in amino acid composition of the N-termini have been identified [26,27].

SPHK function is regulated in a spatial and temporal manner primarily through phosphorylation, but also by the interaction with other molecules [28,29]. However, during basal activity of SPHKs, ubiquitous in cells, no post-translational modifications are required [29,30]. Under physiological conditions SPHKs serve a housekeeping function in the regulation of cell fate. They control a balanced level of pro-apoptotic ceramide and sphingosine, and anti-apoptotic S1P, a phenomenon known as “the sphingolipid rheostat” [31]. Upon stimulation with various cytokines and growth factors, post-translational modifications enhance SPHKs activity. Stimulation leads to increased S1P production and its subsequent action as an intracellular signaling molecule or its release outside of the cell and activation of signaling pathways mediated by S1PRs.

Distinct subcellular localization of SPHK1 and SPHK2 is the main determinant of their divergent function [32]. In unstimulated cells, SPHK1 and SPHK2 are present mainly in a cytosolic form. However, upon stimulation the SPHK1 isoform translocates to the plasma membrane. This process is regulated *via* phosphorylation at Serine 225 (S225) by extracellular signal-regulated kinases 1/2 (ERK1/2), which enhances activity of the enzyme [33]. Another important mechanism that enables SPHK1 membrane relocalization is its calcium-mediated association with calcium- and integrin-binding protein 1 (CIB1) [34]. In general, SPHK1 activity promotes cell proliferation and survival [35]. The polypeptide sequence of SPHK2 contains a nuclear localization signal (NSL) and a nuclear export signal (NES), which determines its nuclear localization. In the nucleus SPHK2 can inhibit DNA synthesis causing cell cycle arrest [36], and can inhibit histone deacetylases altering epigenetic regulation of gene expression [37]. Moreover, it is well established that under stress conditions, SPHK2 is also present in endoplasmatic reticulum (ER), where it stimulates ceramide production aiding the induction of apoptotic cell death [38]. Interestingly, SPHK2 is not present extracellularly, while approximately 8% of the intercellular SPHK1 pool, is secreted outside the cell [39].

1.3. Sphingosine-1-phosphate receptors

Besides the S1P gradient in the body, the spatial distribution of S1P receptors is a major determinant of S1P's versatile role in the cardiovascular system [40]. Among five known GPCRs with a high affinity to S1P, types 1, 2 and 3 are predominantly expressed in cardiovascular tissues, while S1PR4 is characteristic of the lymphatic system and S1PR5 is characteristic of the immune and nervous systems [41]. S1PRs are coupled to specific G protein α subunits, which provides divergent signaling responses. S1PR1 binds exclusively $G\alpha_i$, which upon receptor activation is released and reduces cyclic adenosine 3′,5′-monophosphate (cAMP) level by cyclic adenylase inhibiton [42,43]. $G\alpha_i$ activation leads also to the upregulation of protein kinase C (PKC) isoform α and ε and ERK1/2 signaling [44–46]. In addition to $G\alpha_i$ coupling, S1PR2 and S1PR3 also couple with $G\alpha_q$ and $G\alpha_{12/13}$, which activate phospholipase C (PLC) and RhoA exchange factor signaling respectively [40,41,46].

Cardiomyocytes, cardiac fibroblasts, endothelial cells and vascular smooth muscle cells (VSMCs) demonstrate different patterns of S1PR expression [47]. Although, these cells are characterized by the presence of all three S1PRs, the difference in their expression level determines unique downstream molecular consequences. S1P signaling in cardiomyocytes is predominantly mediated by an abundant presence of S1PR1 [48], while cardiac fibroblast express mainly S1PR3 [49]. VSMCs are characterized by a high S1PR2 and S1PR3 expression, with much lower level of S1PR1 [46]. In contrast, S1PR1 is the main type of receptor expressed by ECs, followed by S1PR3 and at a lessor frequency, S1PR2 [50]. Specific S1P receptor affinity, as well as additional receptor-independent intracellular S1P actions, make the SPHK-S1P axis a complex, yet important signaling pathway in the different cardiovascular compartments.

2. S1P and embryonic development

The circulatory system is the first to develop during embryogenesis in vertebrates and is essential for body function. Importantly, the maintenance of a S1P balance is indispensable for a proper cardiovascular development, and emphasizes the importance of S1P as a signaling molecule (Fig. 1).

A net of newly formed vessels is created by aggregation of endothelial progenitor cells in a process called vasculogenesis. Further expansion of this primitive vascular plexus, involves remodeling, stabilization and maturation to make a complex, fully functional network of vessels [51]. In 2000, Liu and colleagues demonstrated that *S1pr1*-null mice die in utero (between E12.5 and E14.5 day) as a result of severe bleeding related to immaturity of the vasculature [52]. Further studies provided evidence that other S1prs also contribute to vasculature development. Kono et al. showed that triple *S1pr1/S1pr2/S1pr3* knockout mice exhibit an even more severe phenotype as they die earlier than S1pr1-null mice (between E10.5 and E11.5) [53]. Moreover, Mizugishi et al. revealed that *Sphk1/Sphk2*-null mice embryos die prematurely before E13.5 due to inefficient vascularization, as well as due to disturbed neurogenesis [54]. Furthermore, a study by Xiong et al. established that red blood cells (RBCs) are the main source of embryonic S1P necessary for normal vasculogenesis [55].

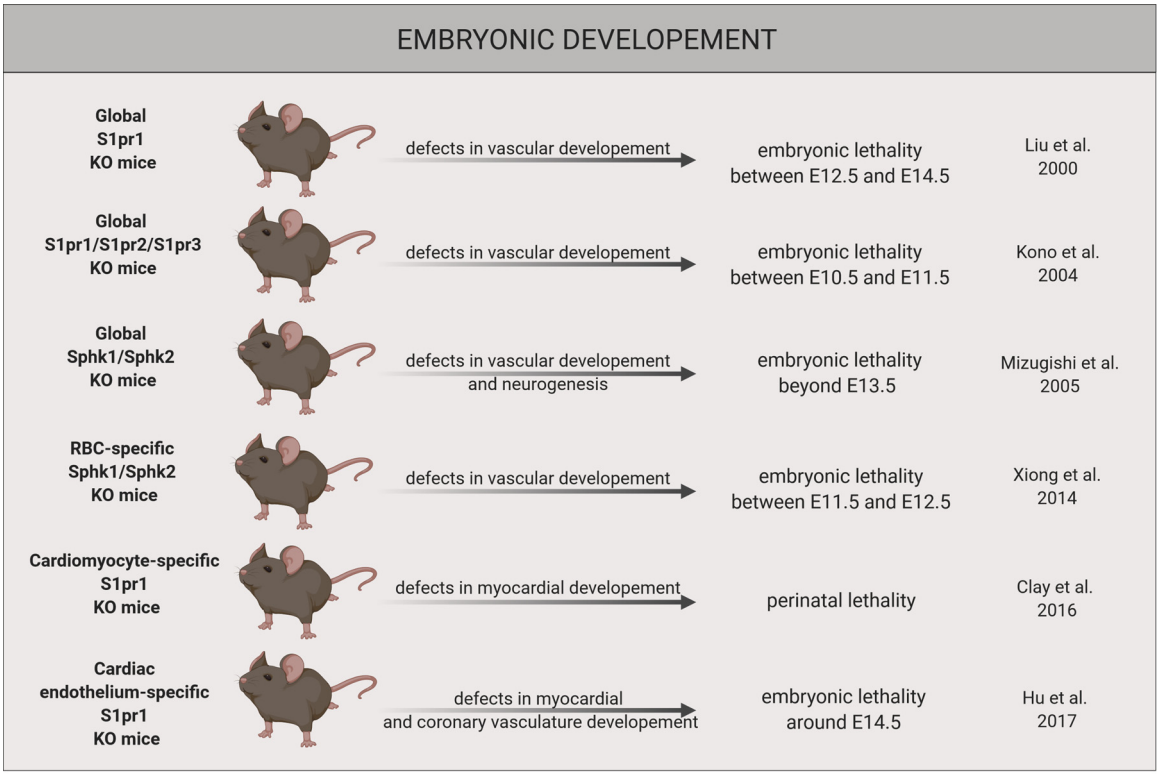

Fig. 1. Sphingosine-1-phosphate (S1P) and the embryonic development.
S1pr - sphingosine-1-phosphate receptor, Sphk – sphingosine kinase, RBC – red blood cell, KO – knockout mice. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

The significance of S1P signaling in the heart is also evident as early as the embryonic stage. Cardiomyocyte-specific knockout of *S1pr1* is perinatally lethal due to ventricular noncompaction with septation defects [56]. Furthermore, cardiac endothelium-specific loss of *S1pr1* is linked to abnormal atrial and ventricular cardiomyocyte development, as well as defects in coronary vasculature formation [57].

3. S1P and postnatal vascular homeostasis

While S1P signaling is essential for vascular development during the embryonic stage, the maintenance of the postnatal S1P balance provides homeostasis for mature blood vessels. Studies have established a multilayered action of S1P in postnatal vascular physiology and pathology (Fig. 2). Investigators have revealed that S1P controls vascular tone, endothelial barrier maintenance and directs lymphocyte trafficking. Therefore the following section focuses on the consequences of S1P dysregulation and signaling during hypertension (HT), atherosclerosis and angiogenesis [24,58,59].

3.1. S1P, vascular tone, lymphocyte trafficking and hypertension

HT is a disease of a multifactorial etiology and has a complex pathophysiology [60]. A chronic increase in blood pressure (BP) has substantial consequences for cardiovascular health and carries a high risk for multi-organ pathology [61]. Vascular resistance and peripheral endothelial dysfunction are classical hallmarks of this disorder. However, besides a well characterized involvement of the kidney and its alteration of the renin-angiotensin-aldosterone system (RAAS), and effects generated from the sympathetic nervous system (SNS), which becomes hyperactivated in HT, a growing body of evidence indicates that chronically increased BP is closely linked with aberrant immune responses (reviewed in (62)). Importantly, all mentioned aspects of HT pathogenesis are, at least partially, controlled by S1P balance.

The effects of S1P on vascular tone are complex and largely dependent on the affected vascular layer. Studies have revealed that S1P promotes both endothelium-dependent vasorelaxation through the activation of S1PR1/3 signaling in ECs, as well as vasoconstriction mediated *via* S1PR2/3 receptors expressed in VSMCs [63–65]. Furthermore, vasoactive properties of S1P depend on various factors such as species, gender, the concentration of S1P, the vascular bed, vessel diameter and spatial distribution of S1P receptors [66]. Mechanistically, receptor-mediated S1P action leads to intracellular Ca^{2+} rise and subsequent calmodulin-dependent myosin light chain kinase (MLCK) activation in VSMCs, or calmodulin-dependent eNOS activation and NO production in ECs. S1P also acts through a Ca^{2+}-independent mechanism, *i.e* the Rho associated coiled-coil containing protein kinase 1 (Rock1) activation which promotes myosin light chain phosphatase (MLCP) phosphorylation resulting in VSMCs contraction. Futhermore, S1P acts through phosphatidylinositol 3-kinases (PI3K)-Akt/protein kinase B (PKB) and their subsequent eNOS phosphorylation in ECs which trigger vasorelaxation [66,67]. Interestingly, while HDL exerts known vasodilatory effect on vessels, Perségol et al. demonstrated that this effect is significantly enhanced by S1P [68]. This suggests a pivotal role of S1P in HDL-mediated vasodilation.

AngII promotes a biphasic Ca^{2+} increase in VSMCs. The first peak results from inositol 1,4,5-tris-triphosphate (IP3) signaling and ER store depletion, which consequently triggers a sustained influx of extracellular Ca^{2+} through store-operated calcium channels (SOCs) in a process called store-operated calcium entry (SOCE). Stromal interacting molecule-1 (Stim1) is a key mediator of SOCE, which after sensing low Ca^{2+} concentrations in the ER, binds and activates plasma membrane proteins, Orai that constitute the pore-forming unit of SOCs. This allows channels opening and extracellular calcium influx. Interestingly, SOCE appears to be an independent mediator of experimental hypertension (for details see [69–71]). Importantly, studies shows that the process of SOCE-mediated extracellular calcium mobilization is regulated by S1P

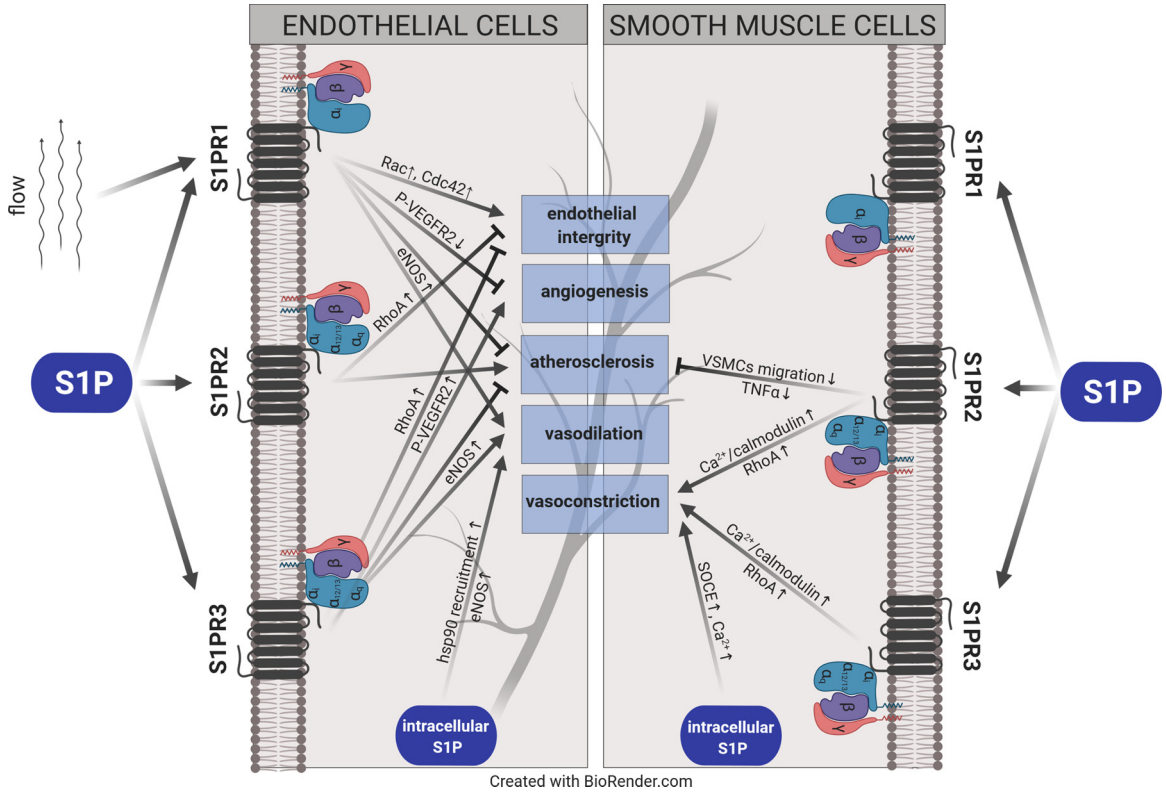

Fig. 2. S1P signaling in the vasculature.
S1PR - sphingosine-1-phosphate receptor, P-VEGFR2- phosphorylated vascular endothelial growth factor receptor 2, eNOS- endothelial nitric oxide synthase, hsp90- heat shock protein 90, SOCE- store operated calcium entry.

in a receptor-independent manner by the direct binding of intracellular S1P to the EF/SAM1 domain of the Stim1 protein [58,72]. Additionally, intracellular S1P may play a role in ECs by promoting the recruitment of heat shock protein 90 (hsp90) to eNOS, leading to increased NO production as previously shown in the endothelium of the rat aorta [73].

Studies investigating vasoactive properties of S1P often demonstrate seemingly opposite conclusions concerning its effect on BP levels and HT development. Early studies demonstrated that intravenous administration of S1P produces a rapid and transient decrease in the mean arterial pressure (MAP) in anesthetized rats. Interestingly, it was recently demonstrated that activation of the S1P/Sphk1/S1pr1 axis is necessary for the rapid BP lowering effect of the endogenous cannabinoid, anandamide in anesthetized mice [74]. However, continuous administration of S1P results in hypertension in conscious rats, as well as in wild-type mice, but not in *S1pr3* knockout mice [75]. Importantly, Cantalupo and colleagues showed that mice lacking transcription factor Nogo-B, which is an inhibitor of the rate limiting step of *de novo* sphingolipid synthesis, are hypotensive and do not develop HT in response to AngII infusion. Additionally, intraperitoneal injection of S1pr1 agonist, SEW2871, also reduced systolic BP of AngII-infused hypertensive mice [76]. In line with the above, S1pr1 receptor activation was identified as a crucial factor of flow-mediated vasodilation and EC-specific *S1pr1* knockout mice were characterized by the increased baseline BP, as well as an elevated BP following AngII infusion [77]. Lately, Swendeman et al. demonstrated that administration of S1P chaperone (ApoM-Fc protein), that is a carrier for plasma S1P, reduces the BP level in AngII-infused hypertensive mice and is accompanied by an increase in plasma nitrite production. This effect is completely abolished after treatment with S1pr1 inhibitor [78]. On the other hand, Lorenz and colleagues showed that mice lacking *S1pr2* exhibit impaired vasoconstriction responses and thus are characterized by reduced peripheral vascular resistance [79]. Crucially, it has been shown that experimental hypertension results in an elevated S1P plasma level [59,80] and that mice with a global deletion of *Sphk1* develop less severe AngII-dependent HT [58,59,80]. Recently, our group has found that pharmacological inhibition of Sphk1 with the selective inhibitor-PF543, improves endothelial function by altering the eNOS phosphorylation status in mesenteric arteries of hypertensive mice. However this effect was independent of BP [81]. Thus, in order to dissect specific, vascular effects of sphingosine kinases, it would be of great value to study EC- and VSMC-specific *Sphk1* and/or *Sphk2* knockout mice and to further characterize autocrine mechanisms of S1P action. Moreover, it can be postulated that specific overexpression of S1pr1 in the endothelium might be potentially beneficial for vascular function and should be examined in animal models of HT.

Recent experimental studies in aged mice suggest that there exist significant sex-dependent differences in S1P-mediated vascular changes [82]. While currently most studies investigate S1P effects in male animals exclusively, there is a need to involve both male and female animals in future *in vivo* studies as sex may significantly affect S1P action.

Besides the effects on vascular tone, S1P directly affects kidney functioning. Graham et al. identified *S1pr1* as one of the candidates for salt-sensitive hypertension of stoke-prone spontaneously hypertensive rats (SHRSP) [83]. Importantly, salt-loaded SHRSP were characterized by a decreased level of kidney S1pr1 as compared to levels in WKY rats. Other studies have shown that S1P affects urinary Na^+ excretion and alters BP level through S1pr1 activation [84,85]. Moreover, S1P protected renal tissue against ischemia/reperfusion injury [86]. Thus, a reduced level of S1pr1 in the kidneys of SHRSP rats may explain the decreased renoprotective effects of S1P in these animals [83].

Emerging evidence from the past decades established a significant contribution of the immune system during the development of HT. Chronic inflammation caused by an accumulation of immune cells in organs regulating BP (such as perivascular fat tissue, kidneys, heart and brain), disrupts physiological homeostasis and may lead to HT [87–91].

Crucially, S1P plays a significant role in the regulation of adaptive immune responses as it promotes naïve T cell survival and is crucial for lymphocyte trafficking [92–94]. S1PR1 expression on T cells and the S1P gradient, which is low in lymphoid organs in comparison to their exit sites, are required as a spatial cue for lymphocyte egress from the thymus and from secondary lymphatic organs before entry into the blood and lymphatic circulation [94–96]. Studies have established that the main contributor to the plasma S1P pool required for lymphocyte trafficking are erythrocytes, while lymph S1P is derived primarily from lymphatic ECs [9,94,96,97]. Sphks-deficient mice are characterized by an upregulated S1pr1 expression in lymphocytes, a lack of S1P and reduced amount of T and B cells in plasma and lymph [9]. Furthermore, mice with the genetic deletion of *S1pr1* in hematopoietic cells display disturbed lymphocyte egress from the thymus and secondary lymphoid organs [98,99].

Importantly, it has been demonstrated that *Sphk2* knockout mice (*Sphk2*$^{-/-}$) are characterized by T cell accumulation in the mesenteric lymph nodes and have a blunted BP level in the hypertensive state as compared to levels in the WT animals, thus Sphk2 has been proposed as a key sphingosine kinase isoform responsible for T cell egress in HT [80]. Recently, Don-Doncow et al. observed that progression of HT is accompanied by S1P and T cells accumulation in the brain which causes neuroinflammation and leads to cognitive impairment. Moreover, genetic *Sphk1* knockout prevented such changes in the brain of hypertensive mice [100].

Among modulators of S1PRs function, FTY720 (also known as Fingolimod) was the first agent with proven immunosuppressive properties [101,102]. Currently, it is a clinically approved drug used in the treatment of multiple sclerosis [103]. FTY720, which is a structural homolog of sphingosine, becomes phosphorylated by Sphk2 and, in this active form, acts as an agonist for S1PR1 (initially) and for S1PR3-5 receptors. However, the ability of FTY720 to cause peripheral lymphopenia results from functional antagonisms towards S1PR1, which promotes receptor internalization and its subsequent degradation in T cells [101,102]. Several studies testing FTY720 action in various animal HT models were conducted, however, they demonstrated seemingly contradictory results. It is important to stress that besides the immunosuppressive properties of FTY720, which may provide protection against HT development, S1pr1 downregulation in ECs is associated with increased endothelial dysfunction (discussed earlier) and may result in exacerbation of HT. Similar to endogenous S1P, FTY720 primarily triggers a transient BP decrease acting through the S1PR1 receptor on ECs, and its subsequent downstream activation of eNOS signaling. However, chronic stimulation with the drug results in S1PR1 internalization, which promotes the binding of plasma S1P to S1PR2 and S1PR3 resulting in vascular contraction [104].

Meissner et al. demonstrated that chronic FTY720 administration, prior HT development, triggers peripheral lymphopenia and thus prevents AngII-induced development of HT. Importantly, authors demonstrated that FTY720 was not effective when administered in the animals with established HT [80]. On the other hand, other studies do not support protective effects of FTY720 in HT *in vivo*. Fryer et al. demonstrated that chronic administration of the drug increases BP in a dose-dependent manner in normotensive rats [105]. Moreover, Spijkers and colleagues confirmed a similar action of the drug in hypertensive rats 24 h after single-dose treatment, although in normotensive animals BP was significantly reduced [106]. Finally, Cantalupo et al. found that chronic FTY720 administration impaired S1P-, Ach-, flow-mediated and endothelium-independent dilation of mesenteric arteries, as well as increased BP of hypertensive mice [77]. Differences regarding results of the above studies may be explained by the differing treatment regimens *e.g.* difference in a dose and frequency of drug administration. Therefore, the exact effects of *in vivo* FTY720 administration on BP should be further investigated in various animal models of HT. It would be of interest to perform an in-depth analysis of molecular mechanisms of the regulation of S1PR1 internalization and degradation in order to find other ways to genetically or pharmacologically modulate receptor activity in different cell types, and particularly in T cells and ECs.

Results supporting the deleterious FTY720 effect on BP *in vivo* are in line with phase III clinical studies which test drug safety and efficacy in multiple sclerosis treatment. It was demonstrated that the incidence of HT among patients receiving FTY720 was significantly higher compared to incidences in those receiving placebo [107]. A recent, large genome-wide association study (GWAS) confirmed that genes involved in S1P signaling affect the level of blood immune cells in humans [108]. Using UK Biobank data, Astle and colleagues demonstrated that single nucleotide polymorphisms (SNPs) in SPHK1 and S1PR1 loci associate with the absolute count of blood lymphoid cells, while SNPs in SPHK2 and S1PR4 loci correlate with the absolute count of, among others cell types, total myeloid cells. Interestingly, among the various major white blood cell populations, only the lymphoid cell count level was associated with coronary heart disease, yet not with chronic kidney disease, using Mendelian Randomization (MR) analysis [108,109]. In line with this, a recent study by Siedlinski et al. found evidence in support of a potential causal, positive effect of blood lymphocyte count on blood pressure indices using observational data and MR approach [110]. Of note, GWAS also supports an association of SNP in the 3′UTR of S1PR2 with BP-related indices, yet the association comes from a locus rich in various genes, including ICAM1 and DNMT1 [111,112]. Thus, it is of future interest to test whether genetic determinants of blood lymphoid cell level and SPHK1, S1PR1 and S1PR2 associate with tissue infiltration of inflammatory cells and/or related clinical outcomes.

3.2. S1P, endothelial barrier and angiogenesis

Endothelial barrier is crucial for the selective transport of fluids and solutes between the blood and the surrounding tissue [113]. Intracellular contractile forces, provided by actin-myosin crosslinking, as well as, cell-cell and cell-matrix interaction which generates tethering forces, are of great importance in the maintenance of vascular wall integrity [114,115]. Additionally, the presence of endothelial glycocalyx (EG), which consists of proteoglycans, hyaluronan, glycoproteins and plasma proteins, and coats the luminal surface of vessels is another important factor in the blood-to-tissue barrier [116]. A sustained increase in endothelial permeability leads to vascular leakage and carries profound consequences such as hemorrhage, edema or inflammation [17]. Reduced endothelial barrier is a hallmark of acute inflammatory diseases such as sepsis and acute lung injury (ALI) [117], promotes cancer cells invasion and metastasis [118], and is an important contributor to atherosclerotic development [24].

It has been established that S1P possesses potent barrier-protective properties [17,119–121]. Garcia and colleagues investigated the effects of S1P in microvascular ECs *in vitro* and demonstrated a dose-dependent increment in transmonolayer electrical resistance [120]. This effect was linked to S1PR1 and S1PR3 signaling, and the downstream activation of small GTPases part of the Rho family which affect cytoskeletal organization [120]. Other studies further confirmed that barrier-enhancing properties of S1P are associated with a positive regulation of adherens junction and tight junction assembly and indicate S1pr1/Rac as a key mediator of S1P action [17]. An *in vivo* study performed by Camerer et al. demonstrated that mice lacking S1P in the plasma, and subjected to anaphylaxis and platelet-activating factor (PAF) or histamine administration, exhibit enhanced vascular leakage resulting in high mortality. Interestingly, the administration of erythrocytes, *i.e.* the main source of S1P in the plasma, restored the endothelial integrity in S1P-deficient mice [122]. Moreover, oral administration of FTY720 inhibited vascular endothelial growth factor (VEGF)-induced vascular leakage in mice [123]. Conversely, S1pr2, S1pr3 and downstream Rho activation was associated with increased vascular permeability both *in vitro* and *in vivo* [124–127]. Interestingly, Sun et al. showed that patients with sepsis or ALI have increased S1PR3 protein levels in the plasma as compared to levels in the control group, thus S1PR3 was

proposed as a novel biomarker for ALI severity [128]. Recently, Reinhard and colleagues demonstrated that S1PR1/$G\alpha_i$/Rac1 and S1PR1/$G\alpha_i$/Cdc42 signaling promotes EC spreading and vascular barrier integrity, while S1PR2/$G\alpha_{12/13}$/RhoA signaling increases endothelial permeability by inducing cell contraction. It was additionally revealed that early activation of RhoA inhibits signaling driven by Rac1 but not Cdc42, thus the rapid increase in endothelial integrity triggered by S1P is provided by the activation of Cdc42 [129]. Crucially, the effect of S1P on vascular permeability strongly depends on its concentration. Studies demonstrated that in physiological conditions S1P acts as a barrier-protective agent, while in higher concentrations (*e.g.* > 5 μM) S1P causes endothelial barrier disruption [17,130,131].

Interestingly, the mechanism of action of S1P closely resembles that of activated protein C (APC), *i.e.* another known barrier enhancing agent [132]. Indeed, studies demonstrated that APC binds to endothelial protein C receptor (EPCR) and mediates PI3K/Akt-dependent phosphorylation of S1pr1 at threonine 236. Moreover, S1pr1 silencing in ECs treated with the barrier disrupting agent- thrombin, reduced APC/Rac1-mediated barrier protection. Importantly, recombinant human APC was tested in clinical trails to treat severe sepsis, however, it eventually failed as it showed the same results as placebo [133].

Several reports have linked S1P with the remodeling of glycocalyx, which covers the vascular endothelium. Early studies demonstrated that plasma albumin stabilizes EG structure and its depletion results in glycocalyx shedding from endothelial surface and disruption of barrier integrity [134,135]. Thus, Zeng and colleagues decided to test whether S1P may be responsible for the stabilizing function of albumin. Indeed, *in vitro* studies showed that S1P acting *via* S1pr1 suppresses the activity of metalloproteinases (MMPs) that mediate EG shedding, and thus may restore the endothelial barrier after albumin depletion [134]. Further investigation revealed that S1P not only stabilizes EG, but is responsible for its synthesis and this process is mediated *via* activation of PI3K signaling [136]. The protective effects of S1P on EG were subsequently confirmed in *ex vivo* treated microvessels isolated from rats [137]. Recently, the same group showed that S1P inhibits tumor cell adhesion to the microvessel walls by regulating EG and vascular permeability [138]. It was also demonstrated that S1P restores inter-endothelial transport, mediated *via* gap junctions by preventing EG shedding and thus, enables communication between ECs *in vitro* [139]. Furthermore, S1P administered during resuscitation following hemorrhagic shock improved endothelial barrier integrity and protected against microvascular leakage in rats [140]. Indeed, S1P is considered as the main contributor to the protective effect of therapeutic plasma administration in patients after trauma-hemorrhagic shock [141].

Altered vascular permeability is linked to aberrant postnatal angiogenesis [113,115]. Angiogenesis is the process of new blood vessel formation from pre-existing ones. Physiologically, it occurs mainly during embryonic development and in adults is restricted to processes such as wound healing, skeletal growth, pregnancy and menstrual cycle. Pathological (excessive) angiogenesis underlies the pathogenesis of cancer and other disorders [142]. Conversely, insufficient blood vessel formation prevents tissue regeneration following myocardial infarction or stroke [143,144]. The master regulators of angiogenesis, hypoxia-inducible factor (HIF) and vascular endothelial growth factor (VEGF) are activated in tissue deprived of oxygen, and mediate neovascularization *via* increasing vascular permeability, induction of EC proliferation, migration and tube formation [145]. Subsequent recruitment of mural cells and deposition of basement membrane provides vessel stabilization and maturation [146].

Studies revealed that S1P counteracts VEGF function and prevents excessive vessel sprouting by sealing the endothelial barrier. S1P prevents vascular endothelial (VE)-cadherin internalization and thus stabilizes endothelial cell adherens junctions *via* S1PR1 [147]. Additionally, S1P/S1PR1 signaling activation downregulates VEGF-induced phosphorylation of VEGF receptor 2 (VEGFR2), ERK1/2 and Akt, while S1PR1 ablation is associated, conversely, with hypersprouting of developing vessels [147]. However, the exact mechanism of angiogenic S1P action still remains to be elucidated, since it is not known if it directly inhibits VEGFR-2 signaling or whether it is a secondary effect of increased VE-cadherin action, which is able to recruit phosphatases to the VEGFR-2 signaling complex. Interestingly, although it was previously shown that S1P/S1pr1 signaling stimulates mural cell recruitment thus stabilizing developing vessels [52], Gaengel et al., as well as Jung et al. argue with this, as they did not observe a significant difference in pericyte coverage of vessels in mice lacking S1pr1 as compared to control [147,148]. Jung and colleagues additionally revealed that blood flow is able to evoke activation of S1pr1 signaling in ECs in a ligand-independent manner both *in vitro* and *in vivo* [148]. In general, it is proposed that VEGF is responsible for vascular network formation, while S1P/S1PR1 signaling in ECs provides vessel stabilization *via* adherens junction formation [149]. Interestingly, recent studies have indicated S1P/S1PR3-mediated VEGFR2 activation as the mechanism of pro-angiogenic effects of HDL [150].

Lately, it has been shown that *Sphk1* knockout mice exhibit delayed skin wound healing as compared to wild-type animals due to impaired angiogenesis and recruitment of inflammatory cells. In line with this, *Sphk1* overexpression was associated with improved wound closure and less scaring. Interestingly, it was shown that wounds of *S1pr2* knockout mice healed significantly faster than those of wild-type mice, where S1pr2 expression increased at the end of wound healing in order to inhibit S1pr1-mediated wound closure and to prepare the wound for the remodeling processes [151].

Excessive angiogenesis is a feature of certain types of vascular eye diseases. It has been shown that *S1pr2* knockout mice exhibit reduced pathological neovascularization of the retina in a model of retinopathy of prematurity [152]. Furthermore, antibody that neutralized S1P inhibited angiogenesis and sub-retinal fibrosis and was suggested as potential future treatment for exudative age-related macular degeneration [153]. In addition, pathological neovascularization is necessary for tumor growth and provides a route for cancer cell spread. Advances and current knowledge of the role of S1P in tumor angiogenesis were recently reviewed by Hisano et al. [149]. It is postulated that S1P signaling has a proangiogenic role during tumor formation and may serve as a promising target in future cancer therapies. S1P-related drugs are currently being tested in clinical trials [154]. Understanding S1P action in angiogenic recovery after myocardial infarction or stroke is still poorly understood, thus it represents an interesting avenue for future studies.

3.3. S1P and atherosclerosis

Vascular dysfunction due to impaired endothelial vasodilation, increased vascular permeability, oxidative stress and inflammation precedes development and drives the progression of atherosclerosis, which is characterized by hardening and subsequent narrowing of the arteries and the formation of cholesterol-rich plaques in the vessel wall [155,156]. Atherosclerosis is linked to dyslipidemia including increased plasma level of triglycerides and apoB-containing lipoproteins such as LDL, intermediate-density lipoprotein (IDL) and VLDL, known as atherogenic, and decreased anti-atherogenic HDL [157,158]. Except for the known role of HDL in reverse cholesterol transport, which helps maintain cholesterol balance in the body, HDL is considered to be an anti-inflammatory, anti-oxidative, anti-thrombotic, pro-angiogenic and vasorelaxant factor [159].

Association between S1P and atherosclerosis still remains to be fully understood. This is due to the fact that, as emphasized earlier, S1P action depends on the plasma S1P carrier and S1P receptor downstream signaling. S1P/S1pr1/S1pr3 axis activation enhances endothelial barrier and endothelial cell-cell junctions [147] and promotes vasorelaxation *via* eNOS activation [67] and thus is considered to be anti-atherosclerotic. Interestingly, HDL vasodilatory properties are inhibited in *S1pr3* knockout mice, which supports the notion that S1P plays a

central role in HDL action [65]. Furthermore, HDL-associated S1P prevented apoptosis of ECs [160,161]. It was also shown that the HDL/apoM carrier strengthened agonist properties of S1P towards anti-atherosclerotic S1pr1 signaling, while albumin-carried -S1P activates S1pr1 to a limited degree [24]. Another important feature of atherosclerosis is inflammation initiated by monocytes, which recognize adhesion molecules presented on the surface of the endothelium and are recruited to the subendothelial space [162,163]. In most studies S1P is considered to enhance the expression of adhesion molecules [164]. However, other studies have reported that S1P suppresses the process of monocyte adhesion [165,166] and this effect could be mediated by integrin rearrangement in ECs [165]. Additionally, it was recently shown that S1P, as well as HDL-bound S1P acting *via* S1PR2/3 promote signal transducer and activator of transcription 3 (Stat3) and survivin expression and thus reduces macrophage apoptosis. Such effects may be beneficial, as sustained death of macrophages in late atherosclerotic lesions is associated with accelerated disease progression [167]. Additionally, Tamama et al. showed that HDL-bound S1P inhibits VSMCs migration and thus affects plaque stability, while its effects on VSMCs proliferation remains controversial [168]. Recently, Keul and colleagues found that HDL-associated S1P acting *via* S1PR2 exerts anti-inflammatory properties in VSMCs due to inhibition of tumor necrosis factor-α (TNF-α) signaling [169]. Similarly, apoM-bound S1P inhibited inflammation in ECs *via* S1PR2-mediated activation of PI3K/Akt signaling [170]. Pro-angiogenic S1P properties might be related to S1P-mediated chemotaxis of lymphocytes, NK cells, monocytes and macrophages and to its pro-thrombotic properties [24,171]. However, mice deficient in the LDL receptor, fed a high cholesterol diet and administered a sphingosine kinase inhibitor, SKI-II, developed more severe atherosclerosis than these receiving placebo [172]. In line with this, Feuerborn et al. showed that elevation of endogenous S1P alleviates atherosclerosis in LDL receptor-deficient mice [15]. In summary, on the basis of studies utilizing animal models with specific, genetic *S1pr* deletion or given a S1pr agonist, it might be concluded that the effects of S1P are mostly anti-atherosclerotic when mediated *via* S1pr1 and S1pr3 and possibly pro-atherosclerotic when mediated *via* S1pr2 [24,173].

Crucially, patients with coronary artery disease (CAD) are characterized by reduced S1P content in HDL as compared to healthy individuals [174] and it was reported that S1P-loading improves protective HDL signaling in the endothelium [175]. Moreover, therapeutic S1P-loading of CAD-HDL restored HDL function in VSMCs [169].

In conclusion, S1P is an important mediator of various vascular processes and the complexity of S1P actions in regulating vascular tone, endothelial permeability, angiogenesis, hypertension and atherosclerosis certainly requires further investigation. However, the overall conclusion emerges that signaling through S1P type 1 receptor seems to be particularly beneficial in the vasculature as it improves endothelial function, strengthens endothelial barrier integrity, inhibits aberrant angiogenesis and possesses anti-atherosclerotic properties.

4. S1P and postnatal cardiac homeostasis

Numerous studies have established both physiological and pathophysiological roles of S1P in both acute cardiac responses (cardiac inotropy and chronotropy), as well as in chronic processes (such as apoptosis and hypertrophy) occurring in the cardiac tissue (Fig. 3).

4.1. S1P and cardiac contractility

The heart is an autonomous organ that does not require external stimuli to generate or conduct an electrical impulse causing atria and ventricles to contract. However, cardiac innervation by sympathetic adrenergic nerves and parasympathetic cholinergic nerves affects the excitability and conductivity of cardiac muscle, as well as the frequency and the force of contraction, by changes in intracellular calcium concentration [176]. Norepinephrine, a neurotransmitter released from the sympathetic nerve endings, binds to β-adrenergic receptors on cardiac cells and promotes an increase in heart rate (a positive chronotropic effect) and in cardiac contractility (a positive inotropic effect). Parasympathetic signaling, mediated *via* acetylcholine and muscarinic receptors, results in opposite cardiac effects *i.e.* lower heart rate and reduced cardiac contractility [177].

It has been established that S1P acting through GPCRs can modulate Ca^{2+} handling by activating specific G-protein signaling. Indeed, Landeen et al., as well as Means et al. demonstrated that S1P affects cardiac muscle contraction. Studies show that in adult mouse ventricular myocytes, S1P evokes negative inotropic effects associated with decreased myocyte shortening [49,178]. Authors suggested that activation of S1pr1 (with a minor role of S1pr3), and thus $G\alpha_i$ protein signaling, antagonizes β-adrenergic responses by inhibiting adenylyl cyclase/cAMP-associated decrease in L-type calcium channel current (I_{CaL}). Additionally, $G_{\beta\gamma}$ subunit release results in an increase in outward K^+ current (I_{KAch}) and shortens the duration of the action potential, which in turn decreases Ca^{2+} influx and further explains the negative inotropic effect of S1P. The importance of S1pr1 signaling in mediating negative inotropy was further confirmed with the use of cardiomyocyte-specific *S1pr1* knockout mice [179].

S1P also acts as a negative chronotropic agent affecting heart rate. Early studies have demonstrated that S1pr3 specifically mediates transient bradycardia *in vivo* [180]. Administration of non-specific S1P receptor agonists induced bradycardia in wild type mice, however, such an effect was not observed in *S1pr3* knockout mice. In line with this, S1pr1 agonist treatment did not result in alteration of the heart rate. However, recent studies demonstrated S1pr1 activation as a main determinant of the bradycardic effect in rats and humans [104,105,181]. Importantly, FTY720 is known to produce bradycardia as a side effect [107,182]. The bradycardic effect of S1P or FTY720 action is dependent on the G-protein–coupled inwardly rectifying potassium (GIRK) channels activation, which triggers membrane hyperpolarization and transiently reduces excitability [104,183]. Additionally, as shown by Racca et al., patients receiving FTY720 have reduced left ventricular systolic function [184]. Taking this into account, there exists a need to further improve pharmacological modulators of S1P signaling to avoid deleterious cardiac effects [185–187]. A second-generation compound, Siponimod (BAF312), a selective agonist of S1pr1 and S1pr5 receptors has been recently approved by FDA for the treatment of secondary progressive multiple sclerosis. However, despite the fact that BAF312 does not activate S1pr3 signaling, it still reduces heart rate, although this was mitigated by the novel dose titration scheme [185,188]. Crucially, other new generation S1PR-targeting agents (*e.g.* Ozanimod) are now being tested in clinical trials and demonstrate potent therapeutic effects in multiple sclerosis and other autoimmune diseases without clinically significant heart rate reduction [154,189].

Nonetheless, it should be noted that there exists a significant risk of adverse cardiac effects associated with systemic administration of S1P signaling modulators.

4.2. S1P, cardiac hypertrophy and fibrosis

Cardiac hypertrophy is an adaptive mechanism of the heart responding to environmental changes. Physiological hypertrophy is associated with normal or increased cardiac function, while pathological hypertrophy occurs as a consequence of prolonged and abnormal hemodynamic stress or myocardial infarction, and is accompanied by systolic and diastolic dysfunction and eventually progresses to heart failure [190,191]. Morphological thickening of the cardiac walls and septum results in the loss of chamber area. Thickening is caused by cardiomyocyte growth, enhanced proliferation and conversion of cardiac fibroblast to myofibroblasts, as well as interstitial fibrosis due to excessive production of extracellular matrix (ECM) [192]. Death of cardiac myocytes is a hallmark of the transition to a decompensatory stage, which is characterized by thinning of the cardiac wall and

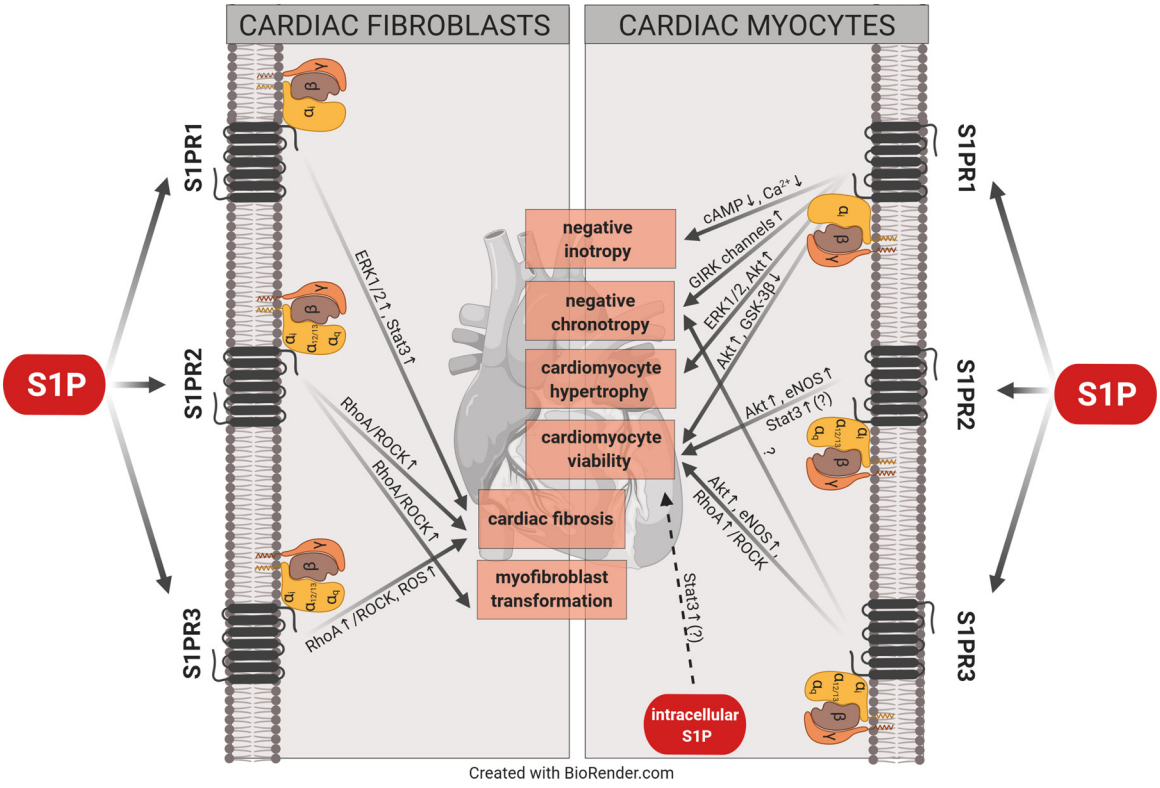

Fig. 3. S1P signaling in the heart.
S1PR - sphingosine-1-phosphate receptor, ERK1/2- extracellular signal-regulated kinases 1/2; Stat3- signal transducer and activator of transcription 3; ROS- reactive oxygen species; cAMP- cyclic adenosine 3′,5′-monophosphate; GIRK- G-protein–coupled inwardly rectifying potassium channels; GSK-3β- glycogen synthase kinase-3β; eNOS- endothelial nitric oxide synthase.

ventricular dilation [190].

The first *in vitro* studies provide conflicting information concerning the effect of S1P on cardiomyocyte hypertrophy. While Sekiguchi et al. did not observe difference in the cardiac myocyte size after S1P stimulation [193], another study by Robert et al. revealed that S1P significantly enhances cardiomyocyte hypertrophy, specifically by activating S1pr1/Gα_i, and downstream ERK1/2, p38, JNK, Akt and Rho signaling [194]. *In vitro* studies in cardiac fibroblasts demonstrated that S1P plays an important role in myofibroblast transformation and regulates TGF-β-induced production of ECM proteins through S1pr2/G$\alpha_{12/13}$ and Rho kinase signaling activation [195]. In line with this, treatment of mouse cardiac fibroblasts with apelin significantly reduced TGF-β dependent fibroblast activation and collagen production by the inhibition of Sphk1 [196]. *In vivo* studies demonstrated that in basal conditions, mice treated with S1P were characterized by marked cardiac myocyte hypertrophy accompanied by an upregulation in the cardiac hypertrophy marker, atrial natriuretic peptide (ANP), and such effects were not dependent on BP [197]. On the other hand, Zhang et al. demonstrated that mice lacking Nogo-A/B systemically or specifically in ECs, which are characterized by increased local S1P production, are resistant to the cardiac hypertrophy and dysfunction following transverse aortic constriction (TAC) [198]. Moreover, S1P treatment prevented TAC-induced cardiac hypertrophy *via* downregulation of histone deacetylase-2 activity and upregulation of anti-hypertrophic transcription factor, Krüppel-like factor 4 (KLF4) [199]. Crucially, studies performed by Siedlinski et al. revealed a significant reduction of cardiac mass in *Sphk1* knockout mice with no significant changes in cardiac fibrosis following 2 weeks of AngII infusion as compared to changes in wild type mice [59]. Furthermore, recently this finding was supported by a study demonstrating that pharmacological inhibition of Sphk1, using selective inhibitor PF543, protected AngII-infused hypertensive mice against development of cardiac hypertrophy without significant effects on cardiac fibrosis. Mechanisms of PF543 action could be partially mediated by the downregulation of cardiac S1pr1, Rock1, Stat3, PKC and ERK1/2 signaling [81]. Interestingly, transgenic mice overexpressing *Sphk1* were characterized by increased cardiac interstitial fibrosis with no effect on cardiomyocyte hypertrophy, which was dependent on S1pr3, *i.e.* the most abundant type of S1P receptor expressed by cardiac fibroblasts, RhoA signaling activation and increased reactive oxygen species (ROS) production, but was independent of AngII type 1 receptor (AT_1) signaling [200]. Furthermore, cardiac fibroblast-specific overexpression of *S1pr1* in mice resulted in increased fibrosis, as well as hypertrophy mediated by Stat3 signaling and interleukin 6 (Il-6) production [201]. Importantly, Liu and colleagues demonstrated that FTY720, is able to reverse an existing pressure overload-induced cardiac hypertrophy and associated fibrosis and improves cardiac performance by inhibiting NFAT signaling in cardiomyocytes and by reducing periostin expression in the ECM [202]. Thus, FTY720 is now considered as a promising new approach in the treatment of heart hypertrophic/fibrotic disease which may ultimately progress to heart failure.

Human study demonstrated that patients with Fabry disease, which is linked to abnormal heart morphology, had significantly higher S1P plasma levels, which positively correlated with left ventricular mass index. Thus, authors proposed S1P as a marker for cardiac remodeling in Fabry disease [197]. Since Sphk1 expression and S1P level are elevated in hypertensive [59] or post-myocardial infarction hearts [203], it would be of great value to investigate changes occurring in the cardiac sphingolipidome following genetic Sphk1 inhibition and whether these changes associate with pathological cardiac remodeling.

4.3. S1P, myocardial infarction and heart failure

Myocardial infarction (MI), is characterized by reduced or blocked

coronary blood flow causing oxygen deprivation of the heart muscle and subsequent death of cardiac cells. The most common cause of MI is rupture of an atherosclerotic plaque formed during CAD [204]. Over the past decades studies revealed that S1P (or HDL-bound S1P) possesses cardioprotective properties and particularly protect cardiomyocytes against apoptosis. In 2001, Karliner et al. demonstrated that exogenously supplied S1P, as well as Sphk activation by ganglioside GM-1, prevented hypoxia-induced death of neonatal rat cardiac myocytes [205]. This effect was confirmed in an adult mouse cardiac myocyte study which also implicated that S1P-mediated apoptosis inhibition was dependent on S1pr1 downstream activation of Akt, inhibition of glycogen synthase kinase-3β (GSK-3β) and reduction of cytochrome c release from the mitochondria [48]. *Ex vivo* experiments performed by Lecour et al. on isolated perfused rat hearts undergoing regional ischemia/reperfusion (I/R), revealed for the first time that S1P has cardioprotective, infarct-sparing effects [206]. The same was shown in isolated perfused mouse hearts undergoing global I/R. Exogenous and endogenous S1P protected cardiac muscle from ischemic injury and the effect of the latter was partially mediated by PKCε [207]. However, S1pr1 agonist, SEW2781, was not able to protect rat hearts against global ischemia *ex vivo* with the same effectiveness as S1P. *In vivo* studies utilizing transgenic mice overexpressing *Sphk1* showed significantly reduced infarct size following ligation of the left anterior descending coronary artery (LAD) [200]. Accordingly, *Sphk1* knockout mice were more sensitive to I/R injury and the protective effects of ischemic pre- and postconditioning were impaired in these mice [208–210]. Lately, Keul et al. in studies using cardiomyocyte-specific *S1pr1* knockout mice showed that S1pr1 is crucial for S1P-mediated ischemic preconditioning. However, in basal conditions, infarct size was similar in both, *S1pr1* knockout and in wild type mouse groups [179]. Additionally, a recent study by Kuang el al. has revealed that endothelium-specific loss of *S1pr1* reduces reparative $F4/80^{+}Ly6c^{low}$ macrophage proliferation and thus exacerbates cardiac remodeling and aggravates cardiac dysfunction after IR injury in mice [211]. This emphasizes the role of coronary microvasculature as an additional target for cardioprotection, beyond protection of cardiomyocytes [212,213].

Several reports demonstrated that it is S1pr2/S1pr3 rather than S1pr1 signaling that provides cardioprotection after I/R injury. For instance, Theilmeier et al. found that HDL-associated S1P protects the heart against I/R-induced damage through NO signaling and this effect was not observed in *S1pr3* knockout mice [214]. Furthermore, Means et al. demonstrated that in *S1pr2* and *S1pr3* double knockout mice infarct size was significantly increased following an ischemic insult as compared to infart size in wild type mice. Mechanistically, the cardioprotective effect of S1P were dependent on Akt/eNOS activation [40,41,215,216]. Additionally, *ex vivo* and *in vivo* studies by Morel et al. revealed an important role of intracellular signaling *via* connexin 43 in a S1pr2/S1pr3 mediated cardioprotection against I/R injury [217]. Another study by Yung and colleagues indicates RhoA signaling as an alternative mechanism downstream of S1pr3 and $G\alpha_{13}$ protein activation [218].

Importantly, cardioprotective effects of S1P also depend on two important pathways that converge to provide cardioprotection after ischemic insult, *i.e.* the Survivor Activating Factor Enhancement (SAFE) and the Reperfusion Injury Salvage Kinase (RISK) pathways, which are activated by protective ischemic pre- and postconditioning, as well as by pharmacological mimetics of ischemic conditioning [25,219,220]. The first pathway involves TNFα-induced Stat3 activation, and the latter is mediated *via* Akt/ERK1/2 signaling. In 2010, Kelly et al. showed that pretreatment with ethanolamine, which is a metabolite of S1P, decreases the infarct size in rats and mice subjected to I/R and activates cardioprotective Stat3 signaling [221]. Subsequent studies demonstrated that S1P administrated at the onset of reperfusion following ischemia reduces the infarct size in wild type mice, however genetic and/or pharmacological loss of TNFα or Stat3 prevented such changes. Furthermore, Akt inhibition also abolished the infarct-sparing effects of S1P. Upregulated signaling *via* SAFE and RISK pathways resulted in inactivation of pro-apoptotic and pro-hypertrophic transcription factor, forkhead box protein O1 (FOXO-1) [222]. Similarly, other studies demonstrate Stat3 signaling as a mediator of protective S1P preconditioning [223]. Based on research by Theilmayer et al., who demonstrated that pre-treatment with human native HDL and sole S1P (unbound to HDL) protected mice against reperfusion injury [214], Brulhart-Meynet et al. proposed an addition of S1P to a synthetic, reconstituted HDL (rHDL) [224], and administration of such enriched rHDL at the time of reperfusion (post-ischemic treatment) [225]. Results revealed that rHDL containing S1P mimics the effect of native HDL (both *ex vivo* and *in vivo*), whereas rHDL in a basic composition is not sufficient to protect against IR injury. Additionally, rHDL-S1P treatment was accompanied by the activation of prosurvival ERK1/2, Stat3 and Akt signaling (225). It is unclear whether S1PR-dependent signaling is required for RISK and SAFE-mediated cardioprotective S1P/HDL actions. Currently, S1PR2 receptor is proposed to be a major mediator, however other receptors may be involved. Additionally, studies indicate that protective TNF signaling might require intracellular S1P [25].

Valuable results are also provided by studies focusing on degradation of S1P by lyase (SPL) in the ischemic cardiac tissue. *Ex vivo* studies demonstrate that the activity of SPL is induced by ischemia in the heart, and that mice lacking SPL are characterized by an increased cardiac S1P level, decreased infarct size and improved functional recovery after I/R injury. Furthermore, FDA-approved food additive, tetrahydroxybutylimidazole (THI), which is known to inhibit SPL, was tested in an *ex vivo* mice I/R model and exhibited similar advantageous properties [226]. In contrast, *in vivo* studies by Zhang et al. revealed that THI treatment of mice following LAD ligation procedure, increased the level of cardiac S1P, however it had an opposing effect on cardiac function and remodeling [203].

Additionally, Zhang et al. showed that pharmacological inhibition of Sphk1 improves left ventricular ejection fraction (LVEF) in post-MI mice [203]. While, following ligation of the LAD artery, Sphk1 activity, S1P level and S1pr1 expression were increased in the cardiac tissue. Treatment with a selective Sphk1 inhibitor, PF543, prevented Sphk1/S1P/S1pr1 pathway activation and upregulation of the cardiac remodeling markers such as brain natriuretic peptide (BNP), ANP and β myosin heavy chain (β-MHC). Accordingly, S1pr1 signaling disruption by FTY720 treatment in post-MI mice also resulted in significant improvement of cardiac function and remodeling, and was associated with inhibition of post-MI inflammation. Thus, authors proposed using FTY720 as a post-MI treatment [203]. In line with the above, Santos-Gallego et al. demonstrated that FTY720 preserves myocardial function following MI in pigs [227].

Quantification of S1P content after MI in human plasma samples revealed a significant decrease as compared to controls and low levels persisted for at least one month after MI. However, it remains unresolved whether the observed post-MI S1P decrease in plasma is a consequence of myocardial infarction itself or/and the result of antiplatelet therapy that was also given to the patients [228,229]. Importantly, recently Polzin and colleagues demonstrated a negative correlation of S1P plasma level with LVEF and dyspnea in patients with ischemic heart disease [230].

Heart failure (HF) is a complex clinical state characterized by insufficient blood supply of the end organs and of peripheral tissues. HF develops following cardiac hypertrophy and/or myocardial infarction and is associated with chronic stimulation of β-adrenergic signaling in cardiac tissue. Recent studies by Cannavo et al. showed for the first time a direct interaction between β1 adrenergic receptor (β1AR) and S1pr1 [43]. Stimulation of β1AR resulted in the downregulation of the plasma membrane level of S1pr1, whereas S1pr1 agonists promoted downregulation of β1AR. The above study indicated that rats with HF had lower levels of circulating S1P and Sphk1 and downregulated expression of S1pr1 in post-MI left ventricular tissue. Thus, Cannavo et al. proposed *S1pr1* gene delivery to prevent left ventricular HF. Indeed, in

post-MI rats direct intramyocardial injection of adenoviral vectors containing *S1pr1* gene ameliorated cardiac function (by increasing LVEF) and reversed maladaptive ventricular dilation by promoting a compensatory hypertrophic response [43]. Unlike in chronic HF, symptoms of acute HF may occur suddenly [231]. Recent *ex vivo* studies in rats demonstrated that S1P administered during recovery after hypotensive *de novo* acute HF, improves the pacemaker ability of the heart and this may be partially mediated by Stat3 signaling [232].

In summary, the mechanism of S1P action in cardiac physiology and pathology is highly sophisticated since S1P affects many different processes that control overall heart function. Although in the case of acute cardiac responses S1P action seems to be only associated with negative inotropy and negative chronotropy, the effects of S1P in chronic cardiac processes are far more complex. In general, S1P is considered to have cardioprotective properties as most studies revealed that it improves cardiomyocyte viability, protects against ischemic injury and might be beneficial in HF. On the other hand, S1P was shown to possess pro-hypertrophic properties as well. Thus, it should be further investigated in long term studies whether S1P signaling in the heart, exposed to stress conditions, prevents or rather drives the progression to HF. Future studies should therefore carefully define the characteristics of the condition/disease model and should determine the specific stage and severity of HF progression, where S1P signaling modulation is tested.

5. Summary

In conclusion, S1P affects the function of the cardiovascular system on multiple levels. Given the fact that S1P acts as an intracellular signaling molecule or as a ligand for various receptors differentially expressed on the cell and tissue level, and affects most processes that are crucial for a functioning cardiovascular system, it is challenging to dissect a specific molecular mechanism that translates into observed phenotypic change. Thus, in order to accomplish this, future research should use more targeted approaches to avoid introducing systemic changes in S1P metabolism and signaling. Currently, modern pharmacological tools such as biased agonist of S1PRs, S1P neutralizing agents, transporter modulators, chaperone-mimicking agents and others, are being developed [154]. Therefore we might be able to effectively use the potential of S1P in the treatment of cardiovascular diseases in the near future.

Submission declaration

All authors have read and approved the submission of the manuscript; the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language, except as an abstract.

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Declaration of Competing Interest

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) the work.

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